REMARKS

Upon entry of the present amendment claims 2-12, 17, 44-47 and 51-59 will be pending in the application. Claims 3-5, 7 and 9 remain withdrawn from consideration under 37 C.F.R. 1.42(b) pursuant to the election of species KRRLIFSK ***with traverse*** in Paper No. 10, but are entitled to consideration upon allowance of the elected claims. MPEP 803.02. Accordingly, claims 2, 6, 8, 10-12, 17, 44-47 and 51-59 are presently under consideration.

As set forth above, claims 2-9, 44, 45 and 51-56 have now been amended, and new claims 57-59 have been added. Support for new claims 57-59 and the amendment of claims 2, 44 and 45 can be found in the specification, for example at page 11, lines 21-28; at page 12, lines 6-12; and at page 13, lines 5-8. Additional support for these claims and amended claims 3-9 and 51-56 can be found throughout the specification, for example, at page 12, lines 14-22 and page 14, lines 14-24. Accordingly, no new matter has been added. In compliance with 37 CFR 1.121, a marked up version entitled "Version With Markings to Show Changes Made," is attached hereto as Appendix I. In addition, for the Examiner's convenience, all of the pending claims are set forth in Appendix II.

Any amendments to and/or cancellation of the claims should in no way be construed as acquiescence to any of the rejections and was done solely to expedite the prosecution of the application. Applicants reserve the right to pursue the same or similar claims in this or a separate application(s).

Claim Rejections under 35 USC §112, first paragraph

Claims 2, 6, 8, 10-12, 17, 44-47 and 51-56 were rejected on the ground that the specification "does not reasonably provide enablement for a method of identifying a compound which decreases the binding between a derivative or analogue or fragment of p21 and a derivative or analogue of cyclin D1." (Paper No. 21, page 2). Applicants respectfully traverse this rejection.

Independent claims 2, 44 and 45 have been amended and new claims 57-59 have been added to clarify what the Applicants view as their invention. First, reference to the term "analogue" has been deleted from the claim without prejudice to expedite prosecution. Second, the claims have also been amended to specify that the "fragments" used in the claimed invention must be peptide fragments of 40 amino acids or less of p21, and that the term "derivatives" refers

to fragments having a 70% identity with p21 over at least 5 contiguous amino acids. Furthermore, the fragments or derivatives must include one of the sequences or motifs listed in these claims. Contrary to the statement in the Office Action that "Applicants do not disclose any actual or prophetic examples on expected performance parameters of any of the possible muteins [*sic*] of p21 or cyclin D1," the specification teaches that a fragment that comprises one or more of these sequences or motifs is able to bind cyclin D1 and/or Cdk4, and provides numerous working examples of such fragments or derivatives (see, e.g., pages 52-69). Thus, the claims, which are now limited to a clearly defined group of peptides that include the specific sequences or motifs that are shown in the application to bind cyclin D1 and/or Cdk4, are clearly enabled.

The citation of Voet *et al.* in the Office Action as evidence of the general unpredictability of amino acid substitutions on protein function is simply not applicable to the instant invention. Applicants respectfully point out that Voet *et al.* merely teach a specific example where an amino acid substitution has a detrimental effect on protein function. In contrast to Voet *et al.*, Applicants thoroughly characterized the protein interactions between p21 with cyclin D1 and Cdk4. Specifically, Applicants have shown that, for p21, certain peptides based on fragments of the full-length p21 protein, can bind/interact with cyclin D1 and/or cdk4. Specific sequences or motifs required to achieve the effect(s) are disclosed. Furthermore, critical residues that provide the claimed technical effect are identified (see, e.g , page 5, lines 8-15), thus clearly indicating which residues in the motifs can be replaced with other residues and which residues must not be changed. As the independent claims now specify that the p21 fragments or derivatives used in the claimed methods ***must*** include at least one such sequence or motif, it is clear to the skilled artisan that would have no difficulty predicting without undue experimentation which p21 peptide fragments or derivatives would have the desired technical effect of modulating p21 interaction/binding with cyclin D1 and/or Cdk4. The amended claims therefore account for the teaching of Voet *et al.* by clearly indicating the residues that must be included in the fragment or derivative, and the specification reasonably enables the claims by providing evidence of the effects of the sequences or motifs. Accordingly, reconsideration and withdrawal of this rejection is respectfully requested.

Claims 2, 6, 8, 10-12, 17, 44-47 and 51-56 were further rejected on the ground that "the claims encompass proteins having one or more amino acid substitutions, deletions, insertions

and/or additions made to cyclin D1 or p21. The specification and claim[s] do not indicate what distinguishing attributes [are] shared by members of the genus" (Paper No. 21, page 5). Applicants respectfully traverse this rejection.

The amended claims include distinguishing attributes of the members of the genus. The common structural attribute is a peptide fragment of p21 or a derivative of such a fragment, both defined by including specific, defined amino acid motifs. References to analogues have been deleted without prejudice. The amended claims include limits to the extent of amino acid changes to derivatives of the fragments as a percentage identity threshold over a minimal window (as described in the specification on pages 12 and 13). The specification clearly teaches the use of such peptides and the effects of the claimed sequences and motifs when included in p21 fragments. The Applicants therefore respectfully request reconsideration and withdrawal of this rejection in view of the amended claims.

Claim Rejection under 35 U.S.C. 112 second paragraph

Claims 10-11, 17, 46 and47 were rejected as "indefinite in the recitation of the term 'modulates'" (Paper No. 21, page 6). Applicants respectfully traverse this rejection. The term "modulates" is standard term used in the art and is intended to embrace methods that identify either agonists or antagonists. Thus, the term is not indefinite, and withdrawal of this rejection is respectfully requested.

Claim Rejections under 35 U.S.C. 103(a)

Claims 2, 6, 8, 10-12, 44-47 and 51-56 were rejected as being unpatentable over Beach *et al.* (WO 94/09135) in view of Xiong *et al.* (1993) on the ground that "the Beach *et al.* reference contains an enabling disclosure, a suggestion to modify the prior art to produce the claimed invention, and a suggestion that the modification would be successful" (Paper No. 21, page 9). Applicants traverse this rejection.

With regard to establishing proof of obviousness, in *In re O'Farrel,853 F.2d 894, 903(Fed. Cir. 1988)*, cited in the Office Action at page 8, the court stated that the prior art must contain "detailed enabling methodology for practicing the claimed invention, a suggestion to modify the prior art to practice the claimed invention, and evidence suggesting that it would be successful." In this case, the court upheld the decision of the United States Patent and

Trademark Office Board of Patent Appeals and Interferences affirming the patent examiner's final rejection of an application under §103 in view of a published paper by two of the three named coinventors. Specifically, the application contained claims for producing a predetermined protein in bacteria by providing a vector containing an indigenous gene linked to a heterologous gene encoding the predetermined protein. These claims were rejected as obvious over a publication that disclosed a plasmid containing the beta-galactosidase gene fused to a heterologous gene encoding for ribosomal RNA. The publication further disclosed results in which a fused polypeptide was produced, and explicitly pointed out that if one were to insert a heterologous gene coding for a protein into their plasmid, it should produce a "fused protein" consisting of a polypeptide made of beta-galactosidase plus the protein coded for by the inserted gene. *Id. at 901.* The court upheld the rejection for obviousness, concluding that "so much of the appellant's method was revealed in the Polisky reference that making a protein by substituting its gene for the ribosomal RNA gene in Polisky (as suggested by Polisky) would have been obvious to one of ordinary skill in the art at the time that the invention was made." *Id at 902.*

Applying the standard set forth in *In re O'Farrell*, it is abundantly clear that, contrary to the assertions presented in the Office Action, Beach *et al.* do not provide and enabling disclosure. For example, Beach *et al.* do not disclose the association between cyclin D, p21 and cdk4. Rather, Beach *et al.* merely disclose a quaternary complex between p21, cyclin D, cdk4 and PCNA. Moreover, Beach *et al.* do not provide specific details of which element interacts with which other element(s) in the complex. In fact, on page 14, lines 1-3, Beach *et al.* state clearly that pairwise interactions between the complex members *are not known*, and there is no indication whatsoever that p21 interacts directly with cdk4 at all. This point is further emphasized by the fact that the methods of screening, disclosed by Beach *et al.*, involving the complex are directed to detection of inhibition or suppression of cell division, an observable phenotype of the cell, and *not* to detection of *specific* pairwise or ternary molecular interactions between p21 and cyclin D1 and/or cdk4 as set forth in the present claims.

Furthermore, although the position presented in the Office Action is that Beach *et al.* disclose that inhibitors of p21 can interfere with p21 binding to complex members, this is clearly a generalization. There is absolutely no teaching or suggestion in Beach *et al.* to look for inhibitors that specifically disrupt the interaction between fragments of p21 and cyclin D1 and/or

cdk4. The same argument applies to the Beach *et al.* disclosure relating to drugs that alter p21 function, as there is no indication whatsoever by Beach *et al.* of which interaction to disrupt. Furthermore, the screening method mentioned in Beach *et al.* (page 24, line 12 – page 25, line 9) effectively reduces to a method of adding test compounds to cells and monitoring whether or not the cells are transformed. Again, such a method is a mere generalization: look for a test compound that provides an observable phenotype in one cell line, which is not observed in a control cell line. Thus, there is no enabling disclosure regarding which interaction to inhibit let alone how to test for this inhibition.

The conclusion that must be drawn is that there is no detailed enabling methodology to allow the skilled artisan to move from the general statements of Beach *et al.* to the use of specific fragments of p21 that contain specific sequences and motifs proven to mimic specific molecular interactions as disclosed in the instant application. Beach *et al.* do not teach the use of peptides from p21 in a screening method. Beach *et al.* merely suggest, as one of a list of possibilities, that a peptide may be used as an inhibitor. They also suggested that an "agent" may mimic a complex constituent to inhibit or enhance cell division. However, there is no indication of which constituent to mimic, or how this mimicry may be achieved. This is consistent with the lack of any enabling detail in Beach *et al.*, as there are no details of specific interactions between p21 and constituents in the complex, and hence there could be no enabling instructions to target a particular constituent. The authors were simply not in a position to provide any further details, as the disclosure clearly indicates by the statement "[a]lthough the experimental techniques used in this study *do not formally allow* a distinction between the existence of multiple pair-wise interactions between each protein, the data are most simply explained if D cyclin, PCNA, CDK and p21 form a quaternary complex" (p.14, lines 1-3, emphasis added).

Thus, in contrast to the facts presented in *In re O'Farrell* 853 F.2d 894 (Fed. Cir. 1988), Beach *et al.* not only fails to provide a detailed *enabling* disclosure, this publication does not contain any suggesting for modifying the prior art to arrive at the claimed invention which is directed to specific interactions between p21 and cyclin D1 and/or cdk4. Furthermore, the present invention links these interactions to specific fragments of a specific constituent (p21) that, in isolation from the rest of the protein, have a specific effect (e.g. binding to cdk4 and/or cyclin D1).

Although Xiong *et al.* disclose putative roles of p21 and provides the sequence of p21, there is no indication in Xiong *et al.*, Beach *et al.*, or Xiong and Beach combined, to hunt for peptides of p21 that mimic the role of p21, *i.e.*, these references contain no indication to modify the prior art in this way. For example, moving from the entire sequence of p21 to selecting specific sub-sequences and/or critical residues that mimic specific molecular interactions could not possibly be derived from a mere sequence listing of the parent molecule. There is no motivation or suggestion in either of these references to look for such peptides but, if the skilled artisan were to try, there are a huge number of possibilities. However, there is no indication in Xiong *et al.* of the location and size of the binding sequences/motifs, or the critical residues, let alone any teaching that any peptide derived therefrom will be a successful mimic of p21 in the absence of the rest of the sequence (and, possibly, structure). Furthermore, factors such as steric effects and the role of the 3D structure of p21, for example, would have caused the skilled person reasonable doubt whether a fragment of p21 would bind cdk4 and/or cyclin D1. In other words, even if the skilled person would think to search for cdk4 and / or cyclin D1 binding fragments of p21, there would be no reasonable expectation of success in the absence of Applicants' disclosure.

Thus, this rejection appears to based on a review of the prior art in the light of the solution offered by the present invention. For example, the sequence KRRLIFSK, allegedly disclosed in Xiong *et al.*, is actually plucked from the full sequence of p21 in view of the disclosure of the present invention. This constitute impermissible use of hindsight. Any specific solution, once disclosed, could be interpreted as obvious in view of a general statement such as "look for inhibitors that inhibit," with no details as to how to screen for such inhibitors, and which specific interactions they inhibit. The path from the general statement to the specifics of the solution, however, is not obvious in the present invention, as there is no indication in the prior art to use p21 fragments, nor is there any indication of which fragments would be successful. In other words, the specific path to follow to the solution (fragments of p21) cannot be ascertained from Beach *et al.*, nor can the solution itself (the specific sequences / motifs). The independent claims of the present application specify these features in the context of a method for screening for a compound that modulates a specific molecular interaction.

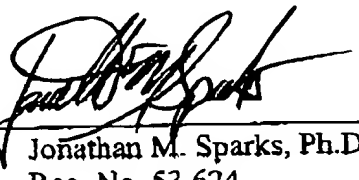
Accordingly, Applicants believe that the claims offer a novel and inventive methods over the prior art, and respectfully request to reconsideration and withdrawal of this rejection.

CONCLUSION

On the basis of the foregoing amendments and remarks, Applicants respectfully submit that the pending claims are in condition for allowance. If a telephone conversation with Applicants' Attorney would expedite prosecution of the above-identified application, the Examiner is invited to call the undersigned at (617) 227-7400.

Date: April 22, 2003

LAHIVE & COCKFIELD, LLP
Attorneys at Law

By: 

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APPENDIX I

VERSION WITH MARKINGS TO SHOW WHERE CHANGES MADE

In the Claims:

Claims 2-9, 44, 45 and 51-56 have been amended, and new claims 57-59 have been added as follows:

2. (AMENDED) A method for identifying a compound which modulates interaction or binding between p21 and cyclin D1, the method including:

(a) bringing into contact a first substance which includes a peptide fragment of 40 amino acids or less of p21, or a derivative ~~or analog~~ thereof having at least 70% identity with p21 over a contiguous sequence of at least 5 amino acids, the fragment or derivative comprising an amino acid sequence selected from the group consisting of:

RERWNFDFVTETPLEGDFAW (peptide 4) (SEQ ID NO:4);

KACRRLFGPVDSEQLSRDCD (peptide 2) (SEQ ID NO:2);

Kxx**R**R**y**F**z****P** (wherein x may be any amino acid, y and z may be hydrophobic, and each of the bold residues may be absent or different); (SEQ ID NO:14)

KRRQTSMTDFYHSKRRLIFS (peptide 10) (SEQ ID NO:10);

KRRQTSATDFYHSKRRLIFS (SEQ ID NO:28);

TSMTDFYHSKRRLIFSKRKP (peptide 11) (SEQ ID NO:11);

KRRLIFSK (SEQ ID NO:23); and

xyLzF (wherein y and z are any amino acid and x is preferably R),

with a second substance comprising cyclin D1, or a derivative ~~or analog~~ thereof having at least 70% identity with cyclin D1 over a contiguous sequence of at least 20 amino acids, and a test compound, under conditions wherein, in the absence of the test compound being an inhibitor of interaction or binding of said first and second substances, said first substance and said second substance interact or bind; and

(b) determining interaction or binding between said first substance and said second substance.

3. (AMENDED) The method according to claim 2, 44 or 45 wherein the fragment, or derivative ~~or analog of p21~~ comprises the amino acid sequence of peptide 4 (SEQ ID NO:4).

4. (AMENDED) The method according to claim 2, 44 or 45 wherein the fragment, or derivative ~~or analog of p21~~ comprises the amino acid sequence KxxRRyF2P (SEQ ID NO:14).

5. (AMENDED) The method according to claim 4 wherein the fragment, or derivative ~~or analog of p21~~ comprises the amino acid sequence of peptide 2 (SEQ ID NO:2).

6. (AMENDED) The method according to claim 2, 44 or 45 wherein the fragment, or derivative ~~or analog of p21~~ comprises the amino acid sequence xyL2F.

7. (AMENDED) The method according to claim 6 the fragment, or derivative ~~or analog of p21~~ comprises the amino acid sequence of peptide 10 (SEQ ID NO:10).

8. (AMENDED) The method according to claim 6 the fragment, or derivative ~~or analog of p21~~ comprises the amino acid sequence KRRLIFSK (SEQ ID NO:23).

9. (AMENDED) The method according to claim 8 wherein the fragment, or derivative ~~or analog of p21~~ comprises the amino acid sequence of peptide 11 (SEQ ID NO:11).

44. (AMENDED) A method for identifying a compound which modulates interaction or binding between p21 and Cdk4, the method including:

(a) bringing into contact a first substance which includes a peptide fragment of 40 amino acids or less of p21, or a derivative ~~or analog~~ thereof having at least 70% identity with p21 over a contiguous sequence of at least 5 amino acids, the fragment or derivative comprising an amino acid sequence selected from the group consisting of:

RERWNFDFVTETPLEGDFAW (peptide 4) (SEQ ID NO:4);

KACRRLFGPVDSEQLSRDCD (peptide 2) (SEQ ID NO:2);

KxxRRyFzP (wherein x may be any amino acid, y and z may be hydrophobic, and each of the bold residues may be absent or different); (SEQ ID NO:14)

KRRQTSMTDFYHSKRRLIFS (peptide 10) (SEQ ID NO:10);

KRRQTSATDFYHSKRRLIFS (SEQ ID NO:28);

TSMTDFYHSKRRLIFSKRKP (peptide 11) (SEQ ID NO:11);

KRRLIFSK (SEQ ID NO:23); and

xyLzF (wherein y and z are any amino acid and x is preferably R),

with a second substance comprising Cdk4 or a derivative ~~or analog~~ thereof having at least 70% identity with Cdk4 over a contiguous sequence of at least 20 amino acids, and a test compound, under conditions wherein, in the absence of the test compound being an inhibitor of interaction or binding of said first and second substances, said first substance and said second substance interact or bind; and

(b) determining interaction or binding between said first substance and said second substance.

45. (AMENDED) A method for identifying a compound which modulates interaction or binding between p21, cyclin D1 and Cdk4, the method including:

(a) bringing into contact a first substance which includes a peptide fragment of 40 amino acids or less of p21, or a derivative ~~or analog~~ thereof having at least 70% identity with p21 over a contiguous sequence of at least 5 amino acids, the fragment or derivative comprising an amino acid sequence selected from the group consisting of:

RERWNFDFVTETPLEGDFAW (peptide 4) (SEQ ID NO:4);

KACRRLFGPVDSEQLSRDCD (peptide 2) (SEQ ID NO:2);

KxxRRyFzP (wherein x may be any amino acid, y and z may be hydrophobic, and each of the bold residues may be absent or different); (SEQ ID NO:14)

KRRQTSMTDFYHSKRRLIFS (peptide 10) (SEQ ID NO:10);

KRRQTSATDFYHSKRRLIFS (SEQ ID NO:28);

TSMTDFYHSKRRLIFSKRKP (peptide 11) (SEQ ID NO:11);

KRRLIFSK (SEQ ID NO:23); and

xyLzF (wherein y and z are any amino acid and x is preferably R),

with a second substance comprising cyclin D1 or a derivative thereof having at least 70% identity with cyclin D1 over a contiguous sequence of at least 20 amino acids, and Cdk4~~,~~ or a derivative ~~or analog~~ thereof having at least 70% identity with Cdk4 over contiguous sequence of at least 20 amino acids, and a test compound, under conditions wherein, in the absence of the test compound being an inhibitor of interaction or binding of said first and second substances, said first substance and said second substance interact or bind; and

(b) determining interaction or binding between said first substance and said second substance.

51. (AMENDED) The method of claim 2, 44 or 45 wherein the peptide fragment or derivative ~~of p21~~ is about 40 amino acids or less.

52. (AMENDED) The method of claim 2, 44 or 45 wherein the peptide fragment or derivative ~~of p21~~ is about 35 amino acids or less.

53. (AMENDED) The method of claim 2, 44 or 45 wherein the peptide fragment or derivative ~~of p21~~ is about 30 amino acids or less.

54. (AMENDED) The method of claim 2, 44 or 45 wherein the peptide fragment or derivative ~~of p21~~ is about 25 amino acids or less.

55. (AMENDED) The method of claim 2, 44 or 45 wherein the peptide fragment or derivative ~~or p21~~ is about 20 amino acids or less.

56. (AMENDED) The method of claim 2, 44 or 45 wherein the peptide fragment or derivative ~~of p21~~ is about 10 amino acids or less.

57. (NEW) A method for identifying a compound which modulates interaction or binding between p21 and cyclin D1, the method including:

(a) bringing into contact a peptide fragment of 40 amino acids or less of p21, or a derivative thereof having at least 70% identity with p21 over a contiguous sequence of at least 5 amino acids, the fragment or derivative comprising an amino acid sequence selected from the group consisting of:

RERWNFDFVTETPLEGDFAW (peptide 4) (SEQ ID NO:4);

KACRRLFGPVDSEQLSRDCD (peptide 2) (SEQ ID NO:2);

Kxx**R**R**y**F**z****P** (wherein x may be any amino acid, y and z may be hydrophobic, and each of the bold residues may be absent or different); (SEQ ID NO:14)

KRRQTSMTDFYHSKRRLIFS (peptide 10) (SEQ ID NO:10);

KRRQTSATDFYHSKRRLIFS (SEQ ID NO:28);

TSMTDFYHSKRRLIFSKRKP (peptide 11) (SEQ ID NO:11);

KRRLIFSK (SEQ ID NO:23); and

xyL$_2$F (wherein y and z are any amino acid and x is preferably R),

with cyclin D1 and a test compound under conditions wherein in the absence of the test compound said fragment or derivative and cyclin D1 interact or bind; and

(b) determining interaction or binding between said fragment or derivative and cyclin D1 in the presence of said test compound.

58. (NEW) A method for identifying a compound which modulates interaction or binding between p21 and Cdk4, the method including:

(a) bringing into contact a peptide fragment of 40 amino acids or less of p21, or a derivative thereof having at least 70% identity with p21 over a contiguous sequence of at least 5 amino acids, the fragment or derivative comprising an amino acid sequence selected from the group consisting of:

RERWNFDFVTETPLEGDFAW (peptide 4) (SEQ ID NO:4);

KACRRLFGPVDSEQLSRDCD (peptide 2) (SEQ ID NO:2);

Kxx**R**R**y**F$_2$**P** (wherein x may be any amino acid, y and z may be hydrophobic, and each of the bold residues may be absent or different); (SEQ ID NO:14)

KRRQTSMTDFYHSKRRLIFS (peptide 10) (SEQ ID NO:10);

KRRQTSATDFYHSKRRLIFS (SEQ ID NO:28);

TSMTDFYHSKRRLIFSKRKP (peptide 11) (SEQ ID NO:11);

KRRLIFSK (SEQ ID NO:23); and

xyLzF (wherein y and z are any amino acid and x is preferably R),

with Cdk4 and a test compound under conditions wherein in the absence of the test compound said fragment or derivative and Cdk4 interact or bind; and

(b) determining interaction or binding between said fragment or derivative and Cdk4 in the presence of said test compound.

59. (NEW) A method for identifying a compound which modulates interaction or binding between p21, cyclin D1 and Cdk4, the method including:

(a) bringing into contact a peptide fragment of 40 amino acids or less of p21, or a derivative thereof having at least 70% identity with p21 over a contiguous sequence of at least 5 amino acids, the fragment or derivative comprising an amino acid sequence selected from the group consisting of:

RERWNFDFVTETPLEGDFAW (peptide 4) (SEQ ID NO:4);

KACRRLFGPVDSEQLSRDCD (peptide 2) (SEQ ID NO:2);

KxxRRyFzP (wherein x may be any amino acid, y and z may be hydrophobic, and each of the bold residues may be absent or different); (SEQ ID NO:14)

KRRQTSMTDFYHSKRRLIFS (peptide 10) (SEQ ID NO:10);

KRRQTSATDFYHSKRRLIFS (SEQ ID NO:28);

TSMTDFYHSKRRLIFSKRKP (peptide 11) (SEQ ID NO:11);

KRRLIFSK (SEQ ID NO:23); and

xyLzF (wherein y and z are any amino acid and x is preferably R),

with a cyclin D1, Cdk4 and a test compound under conditions wherein in the absence of the test compound said fragment or derivative, cyclin D1 and Cdk4 interact or bind; and

(b) determining interaction or binding between said fragment or derivative, cyclin D1 and Cdk4 in the presence of the test compound.

APPENDIX II

PENDING CLAIMS

2. A method for identifying a compound which modulates interaction or binding between p21 and cyclin D1, the method including:

(a) bringing into contact a first substance which includes a peptide fragment of 40 amino acids or less of p21, or a derivative thereof having at least 70% identity with p21 over a contiguous sequence of at least 5 amino acids, the fragment or derivative comprising an amino acid sequence selected from the group consisting of:

RERWNFDFVTETPLEGDFAW (peptide 4) (SEQ ID NO:4);

KACRRLFGPVDSEQLSRDCD (peptide 2) (SEQ ID NO:2);

KxxRRyF2P (wherein x may be any amino acid, y and z may be hydrophobic, and each of the bold residues may be absent or different); (SEQ ID NO:14)

KRRQTSMTDFYHSKRRLIFS (peptide 10) (SEQ ID NO:10);

KRRQTSATDFYHSKRRLIFS (SEQ ID NO:28);

TSMTDFYHSKRRLIFSKRKP (peptide 11) (SEQ ID NO:11);

KRRLIFSK (SEQ ID NO:23); and

xyL2F (wherein y and z are any amino acid and x is preferably R),

with a second substance comprising cyclin D1, or a derivative thereof having at least 70% identity with cyclin D1 over a contiguous sequence of at least 20 amino acids, and a test compound, under conditions wherein, in the absence of the test compound being an inhibitor of interaction or binding of said first and second substances, said first substance and said second substance interact or bind; and

(b) determining interaction or binding between said first substance and said second substance.

3. The method according to claim 2, 44 or 45 wherein the fragment or derivative comprises the amino acid sequence of peptide 4 (SEQ ID NO:4).

4. The method according to claim 2, 44 or 45 wherein the fragment or derivative comprises the amino acid sequence **K**xxRRyFz**P** (SEQ ID NO:14).

5. The method according to claim 4 wherein the fragment or derivative comprises the amino acid sequence of peptide 2 (SEQ ID NO:2).

6. The method according to claim 2, 44 or 45 wherein the fragment or derivative comprises the amino acid sequence xyLzF.

7. The method according to claim 6 wherein the fragment or derivative comprises the amino acid sequence of peptide 10 (SEQ ID NO:10).

8. The method according to claim 6 wherein the fragment or derivative comprises the amino acid sequence KRRLIFSK (SEQ ID NO:23).

9. The method according to claim 8 wherein the fragment or derivative comprises the amino acid sequence of peptide 11 (SEQ ID NO:11).

10. The method according to claim 2, 44 or 45 further comprising testing the ability of the compound to modulate a p21- mediated effect on Cdk4 activity.

11. A method according to claim 10 wherein RB phosphorylation is tested.

12. A method according to claim 2, 44 or 45 wherein induction of G1 cell-cycle arrest is tested.

17. A method comprising obtaining a compound which modulates the interaction or binding between p21 and cyclin D1 in accordance with claim 2, further comprising formulating the compound into a composition including at least one additional component.

44. A method for identifying a compound which modulates interaction or binding between p21 and Cdk4, the method including:

(a) bringing into contact a first substance which includes a peptide fragment of 40 amino acids or less of p21, or a derivative thereof having at least 70% identity with p21 over a contiguous sequence of at least 5 amino acids, the fragment or derivative comprising an amino acid sequence selected from the group consisting of:

RERWNFDFVTETPLEGDFAW (peptide 4) (SEQ ID NO:4);

KACRRLFGPVDSEQLSRDCD (peptide 2) (SEQ ID NO:2);

KxxRRyFzP (wherein x may be any amino acid, y and z may be hydrophobic, and each of the bold residues may be absent or different); (SEQ ID NO:14)

KRRQTSMTDFYHSKRRLIFS (peptide 10) (SEQ ID NO:10);

KRRQTSATDFYHSKRRLIFS (SEQ ID NO:28);

TSMTDFYHSKRRLIFSKRKP (peptide 11) (SEQ ID NO:11);

KRRLIFSK (SEQ ID NO:23); and

xyLzF (wherein y and z are any amino acid and x is preferably R),

with a second substance comprising Cdk4 or a derivative thereof having at least 70% identity with Cdk4 over a contiguous sequence of at least 20 amino acids, and a test compound, under conditions wherein, in the absence of the test compound being an inhibitor of interaction or binding of said first and second substances, said first substance and said second substance interact or bind; and

(b) determining interaction or binding between said first substance and said second substance.

45. A method for identifying a compound which modulates interaction or binding between p21, cyclin D1 and Cdk4, the method including:

(a) bringing into contact a first substance which includes a peptide fragment of 40 amino acids or less of p21, or a derivative thereof having at least 70% identity with p21 over a contiguous sequence of at least 5 amino acids, the fragment or derivative comprising an amino acid sequence selected from the group consisting of:

RERWNFDFVTETPLEGDFAW (peptide 4) (SEQ ID NO:4);

KACRRLFGPVDSEQLSRDCD (peptide 2) (SEQ ID NO:2);

KxxRRyFzP (wherein x may be any amino acid, y and z may be hydrophobic, and each of the bold residues may be absent or different); (SEQ ID NO:14)

KRRQTSMTDFYHSKRRLIFS (peptide 10) (SEQ ID NO:10);

KRRQTSATDFYHSKRRLIFS (SEQ ID NO:28);

TSMTDFYHSKRRLIFSKRKP (peptide 11) (SEQ ID NO:11);

KRRLIFSK (SEQ ID NO:23); and

xyLzF (wherein y and z are any amino acid and x is preferably R),

with a second substance comprising cyclin D1 or a derivative thereof having at least 70% identity with cyclin D1 over a contiguous sequence of at least 20 amino acids, and Cdk4 or a derivative thereof having at least 70% identity with Cdk4 over contiguous sequence of at least 20 amino acids, and a test compound, under conditions wherein, in the absence of the test compound being an inhibitor of interaction or binding of said first and second substances, said first substance and said second substance interact or bind; and

(b) determining interaction or binding between said first substance and said second substance.

46. A method comprising obtaining a compound which modulates the interaction or binding between p21 and Cdk4 in accordance with claim 44, further comprising formulating the compound into a composition including at least one additional component.

47. A method comprising obtaining a compound which modulates the interaction or binding between p21, cyclin D1 and Cdk4 in accordance with claim 45, further comprising formulating the compound into a composition including at least one additional component.

51. The method of claim 2, 44 or 45 wherein the peptide fragment or derivative is about 40 amino acids or less.

52. The method of claim 2, 44 or 45 wherein the peptide fragment or derivative is about 35 amino acids or less.

53. The method of claim 2, 44 or 45 wherein the peptide fragment or derivative is about 30 amino acids or less.

54. The method of claim 2, 44 or 45 wherein the peptide fragment or derivative is about 25 amino acids or less.

55. The method of claim 2, 44 or 45 wherein the peptide fragment or derivative is about 20 amino acids or less.

56. The method of claim 2, 44 or 45 wherein the peptide fragment or derivative is about 10 amino acids or less.

57. A method for identifying a compound which modulates interaction or binding between p21 and cyclin D1, the method including:

(a) bringing into contact a peptide fragment of 40 amino acids or less of p21, or a derivative thereof having at least 70% identity with p21 over a contiguous sequence of at least 5 amino acids, the fragment or derivative comprising an amino acid sequence selected from the group consisting of:

RERWNFDFVTETPLEGDFAW (peptide 4) (SEQ ID NO:4);

KACRRLFGPVDSEQLSRDCD (peptide 2) (SEQ ID NO:2);

KxxRRyFzP (wherein x may be any amino acid, y and z may be hydrophobic, and each of the bold residues may be absent or different); (SEQ ID NO:14)

KRRQTSMTDFYHSKRRLIFS (peptide 10) (SEQ ID NO:10);

KRRQTSATDFYHSKRRLIFS (SEQ ID NO:28);

TSMTDFYHSKRRLIFSKRKP (peptide 11) (SEQ ID NO:11);

KRRLIFSK (SEQ ID NO:23); and

xyLzF (wherein y and z are any amino acid and x is preferably R),

with cyclin D1 and a test compound under conditions wherein in the absence of the test compound said fragment or derivative and cyclin D1 interact or bind; and

(b) determining interaction or binding between said fragment or derivative and cyclin D1 in the presence of said test compound.

58. A method for identifying a compound which modulates interaction or binding between p21 and Cdk4, the method including:

(a) bringing into contact a peptide fragment of 40 amino acids or less of p21, or a derivative thereof having at least 70% identity with p21 over a contiguous sequence of at least 5 amino acids, the fragment or derivative comprising an amino acid sequence selected from the group consisting of:

RERWNFDFVTETPLEGDFAW (peptide 4) (SEQ ID NO:4);

KACRRLFGPVDSEQLSRDCD (peptide 2) (SEQ ID NO:2);

KxxRRyFzP (wherein x may be any amino acid, y and z may be hydrophobic, and each of the bold residues may be absent or different); (SEQ ID NO:14)

KRRQTSMTDFYHSKRRLIFS (peptide 10) (SEQ ID NO:10);

KRRQTSATDFYHSKRRLIFS (SEQ ID NO:28);

TSMTDFYHSKRRLIFSKRKP (peptide 11) (SEQ ID NO:11);

KRRLIFSK (SEQ ID NO:23); and

xyLzF (wherein y and z are any amino acid and x is preferably R),

with Cdk4 and a test compound under conditions wherein in the absence of the test compound said fragment or derivative and Cdk4 interact or bind; and

(b) determining interaction or binding between said fragment or derivative and Cdk4 in the presence of said test compound.

59. A method for identifying a compound which modulates interaction or binding between p21, cyclin D1 and Cdk4, the method including:

(a) bringing into contact a peptide fragment of 40 amino acids or less of p21, or a derivative thereof having at least 70% identity with p21 over a contiguous sequence of at least 5 amino acids, the fragment or derivative comprising an amino acid sequence selected from the group consisting of:

RERWNFDFVTETPLEGDFAW (peptide 4) (SEQ ID NO:4);

KACRRLFGPVDSEQLSRDCD (peptide 2) (SEQ ID NO:2);

KxxRRyFzP (wherein x may be any amino acid, y and z may be hydrophobic, and each of the bold residues may be absent or different); (SEQ ID NO:14)

KRRQTSMTDFYHSKRRLIFS (peptide 10) (SEQ ID NO:10);

KRRQTSATDFYHSKRRLIFS (SEQ ID NO:28);

TSMTDFYHSKRRLIFSKRKP (peptide 11) (SEQ ID NO:11);

KRRLIFSK (SEQ ID NO:23); and

xyLzF (wherein y and z are any amino acid and x is preferably R),

with a cyclin D1, Cdk4 and a test compound under conditions wherein in the absence of the test compound said fragment or derivative, cyclin D1 and Cdk4 interact or bind; and

(b) determining interaction or binding between said fragment or derivative, cyclin D1 and Cdk4 in the presence of the test compound.